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Original Research Article

# An Observational Assessment of the Role of Liver Function as an Indicator of Malaria in Endemic Regions and as a Marker of Disease Severity

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**Conflict of interest: Nil**

**Abstract**

**Aim:** This study was to evaluate the role of liver function as an indicator of malaria in endemic regions and as a marker of disease severity.

**Material & Methods:** This was an observational cross-sectional study conducted in central laboratory, department of pathology, central laboratory, department of biochemistry, and out-patient department, department of medicine over a period of one year, and included 100 microscopy proven malaria positive cases.

**Results:** Among the 80 Plasmodium vivax cases studied, all the three liver function parameters show increased frequency of derangement with increase in parasite load with SGPT and SGOT showing maximum frequency of derangement in severe category, 72.72% (n=16) and 86.36% (n=19) respectively. Among the 20 cases of Plasmodium falciparum studied, also, maximum frequency of derangement is seen in severe parasitemia in all the liver function parameters except SGPT, which shows more derangement in moderate parasitemia with all the cases involved (100%, n=4). In all the cases of malaria studied, all the three parameters show increased frequency of derangement with increase in parasite load, with most frequent derangement seen in severe parasitemia. Bilirubin- 50% (n=18), SGPT- 80.55% (n=29) SGOT-83.33% (n=30). While comparing vivax and falciparum malaria, all the LFTs studied show greater derangement in Plasmodium Falciparum when compared to Plasmodium vivax, with greatest difference seen in bilirubin levels.

**Conclusion:** We concluded that altered liver function in form of hyperbilirubinemia and increased liver enzymes in a patient with acute febrile illness increase the probability of malaria, hence directing the clinician along the correct path of further work-up and accurate treatment.

**Keywords:** Malaria, Aspartate aminotransferases, Alanine aminotransferases, Bilirubin.



## Introduction

Malaria is a major public health problem and led to an estimated 405,000 deaths worldwide in 2018. Most malaria cases were seen in the African Region (213 million or 93%), followed by the South-East Asian Region (3.4%). [1] Approximately 2.48 million malarial cases are reported annually from South Asia, of which 75% cases are contributed by India alone. [2] In India, malaria cases have consistently declined from 2.08 million in 2001 to about 4 lakhs in 2018. [3] Infection with malaria parasites may result in a wide variety of symptoms, ranging from absent or very mild symptoms to severe disease and even death. [4] There is an increasing trend for multiple organ dysfunctions attributed to Plasmodium falciparum as well as Plasmodium vivax. [5-8] Malarial transmission to the human host is established by sporozoites infection to the liver. [9] The malarial sporozoites once injected in blood by the bite of female Anopheles mosquitoes are attached to hepatocytes through receptor for thrombospondin and properdin. [10] Here these sporozoites become mature to form tissue schizonts or become dormant hypnozoites. Clinical features include fever, chills, sweating, headache, vomiting-diarrhoea, abdominal pain and distension, cough, splenomegaly and hepatomegaly. [11,12] Liver involvement in malaria is common in patients of severe malaria and manifests as jaundice, hyperbilirubinemia, hepatomegaly and elevated enzymes (transaminases and alkaline phosphatase). [13] There are inflammatory as well as direct plasmodial effects in the damage to hepatocytes. As serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) is synthesized in the

liver, hence it is possible that initial inflammation of the liver may increase their production due to infection of plasmodium in the liver.

Also, symptoms of malaria associated with vomiting could have caused increased hemoconcentration and led to initial increase in SGOT, SGPT and ALP due to breakdown of the liver cells after infection. [14] The factors leading to severe anemia in malaria are multiple. It may be due to hemolysis, bone marrow dysfunction etc and is proportional to the level of parasitaemia. [15]

Hence the aim of study was to evaluate the role of liver function as an indicator of malaria in endemic regions and as a marker of disease severity.

**Material & Methods**

This was an observational cross-sectional study conducted in central laboratory, department of pathology, central laboratory, department of biochemistry, and out-patient department, department of medicine, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India over a period of one year, and included 100 microscopy proven malaria positive cases. Exclusion criteria consisted of patients with coexistent dengue infection proven by IgG, IgM, NS1 positivity and those patients in whom only gametocytes were detected. We processed the fresh EDTA samples of cases to be included in the study by preparing one thick and one thin smear of each case with Giemsa stain. Peripheral smear positivity for malarial parasite was taken as a gold standard for the diagnosis of malaria. At least 100 fields were examined before reporting the smear as negative. Effort was made to identify the plasmodium species morphology on thin smear and detection and the crude quantitative estimation of parasitemia was done on thick smear. The parasite density was graded by the plus system of WHO and then as scanty, moderate and heavy for our study purpose. [16] The records of serum Bilirubin, SGPT and SGOT for the respective cases were procured from the department of biochemistry.

Sample size of this study was calculated with the help of previously published papers keeping the p value at less than 0.05 and power of study at 80%. All the data was analyzed using appropriate statistical tests. A p value of less than 0.05 was considered significant assuming normal distribution of dependent variables and randomization of independent variables. Qualitative data was expressed in percentage and quantitative data was expressed as mean±standard deviation. Data was entered with the help of Microsoft word and Excel and analyzed by MedCalc software version 12.5.0.

**Results**

**Table 1: Comparison of frequencies of altered liver functions at different parasitemia levels in Plasmodium vivax and Plasmodium falciparum**

| Plasmodium vivax | | | | | | |
|---|---|---|---|---|---|---|
| **Parameters** | **Mild (8)** | **Moderate (50)** | **Severe (22)** | **Mild (%)** | **Moderate (%)** | **Severe (%)** |
| **Bilirubin** | 1 | 13 | 6 | 12.5 | 26 | 27.27 |
| **SGPT** | 4 | 25 | 16 | 50 | 50 | 72.72 |
| **SGOT** | 5 | 32 | 19 | 62.5 | 64 | 86.36 |
| **Plasmodium falciparum** | | | | | | |
| **Parameters** | **Mild (2)** | **Moderate (4)** | **Severe (14)** | **Mild (%)** | **Moderate (%)** | **Severe (%)** |
| **Bilirubin** | 0 | 2 | 12 | 0 | 50 | 85.71 |
| **SGPT** | 1 | 4 | 13 | 50 | 100 | 92.85 |
| **SGOT** | 1 | 3 | 11 | 50 | 75 | 78.57 |

The cut off values for considering the liver function parameters as deranged are taken as follows: serum bilirubin >2 mg/dl, SGPT and SGOT both >40 U/L. Among the 80 Plasmodium vivax cases studied, all the three liver function parameters show increased frequency of derangement with increase in parasite load with SGPT and SGOT showing maximum frequency of derangement in severe category, 72.72% (n=16) and 86.36% (n=19) respectively. However, serum bilirubin shows increased involvement in moderate parasitemia in this study. Among the 20 cases of Plasmodium falciparum studied, also, maximum frequency of derangement is seen in severe parasitemia in all the liver function parameters except SGPT, which shows more derangement in moderate parasitemia with all the cases involved (100%, n=4). This might be due to overall a smaller number of cases of moderate parasitemia in Plasmodium falciparum.

**Table 2: Comparison of frequencies of altered liver function at different parasitemia levels (overall)**

| Parameters | Frequency | | | Percentage (%) | | |
|---|---|---|---|---|---|---|
| | Mild (10) | Moderate (54) | Severe (36) | Mild (%) | Moderate (%) | Severe (%) |
| **Bilirubin** | 1 | 15 | 18 | 10 | 27.77 | 50 |
| **SGPT** | 5 | 29 | 29 | 50 | 53.70 | 80.55 |
| **SGOT** | 6 | 35 | 30 | 60 | 64.81 | 83.33 |

In all the cases of malaria studied, all the three parameters show increased frequency of derangement with increase in parasite load, with most frequent derangement seen in severe parasitemia. Bilirubin- 50% (n=18), SGPT- 80.55% (n=29) SGOT-83.33% (n=30).

**Table 3: Compares frequencies of derangement of liver functions between Plasmodium vivax and Plasmodium falciparum**

| Parameters | Frequency | | | Percentage (%) | | |
|---|---|---|---|---|---|---|
| | Vivax (80) | Falciparum (20) | Total (100) | Vivax (%) | Falciparum (%) | Total (%) |
| **Bilirubin** | 25 | 15 | 40 | 31.25 | 75 | 40 |
| **SGPT** | 46 | 18 | 64 | 57.50 | 90 | 64 |
| **SGOT** | 56 | 17 | 75 | 70 | 85 | 75 |

While comparing vivax and falciparum malaria, all the LFTs studied show greater derangement in Plasmodium Falciparum when compared to Plasmodium vivax, with greatest difference seen in bilirubin levels.

**Table 4: Mean values of liver function at various parasitemia levels**

| Parameters (Mean±SD) | Mild | Moderate | Severe | P value |
|---|---|---|---|---|
| **Bilirubin (mg/dl)** | 1.34±0.86 | 1.75±0.92 | 3.52±4.22 | 0.0004 |
| **SGPT (U/L)** | 42.28±23.27 | 56.34±34.16 | 82.18±54.36 | 0.0022 |
| **SGOT (U/L)** | 54.46±42.12 | 64.58±36.34 | 94.6±56.94 | 0.0048 |

The mean values (±SD) of all the liver functions at various parasitemia levels in malaria. Talking about the liver function parameters, i.e., bilirubin, SGPT and SGOT, all show significant increase in mean values i.e., more derangement with increase in parasitemia (p values being 0.0004, 0.0022 and 0.0048 respectively). All the three parameters show maximum derangement in severe parasitemia with mean values of 3.52, 82.18, and 94.6. While comparing vivax and falciparum malaria, all the LFTs studied show greater derangement in Plasmodium falciparum when compared to Plasmodium vivax, with greatest difference seen in bilirubin levels.

**Table 5: Mean values of liver function in Plasmodium vivax and Plasmodium falciparum**

| Parameters(Mean±SD) | *P. vivax* | *P. falciparum* | P value |
|---|---|---|---|
| **Bilirubin(mg/dl)** | 1.84±1.26 | 4.74±5.25 | <0.0001 |
| **SGPT (U/L)** | 56.84±32.68 | 102.88±62.8 | <0.0001 |
| **SGOT(U/L)** | 65.85±36.44 | 105±62.78 | <0.0001 |

The mean values (±SD) of all the liver functions in Plasmodium vivax and Plasmodium falciparum. In the liver function parameters, all the three parameters were significantly raised in Plasmodium falciparum as compared to Plasmodium vivax with the p values of all three being <0.0001.

## Discussion

For malaria control and eradication to be feasible by the target of 2030 [17,18], there is a necessity to develop novel therapeutic compounds, but no new clinical entities (NCEs) treating blood-stage infections having been developed since artemisinin. [19] The likelihood of artemisinin resistance spreading means that without new medications, significant barriers to control and eradication would remain. [20] As with any drug development, attrition of antimalarial drugs in development pipelines is common and also extremely costly. [21] The World Health Organization (WHO) guidelines reports that severe malaria can cause multi-organ failure and liver damage, with jaundice being relatively common. [22] In non-severe malaria, the guidelines state that hyperbilirubinemia is relatively common, and aminotransferase liver enzymes may be elevated up to 10-fold, but signs of liver failure are extremely rare.

Among the 80 Plasmodium vivax cases studied, all the three liver function parameters show increased frequency of derangement with increase in parasite load with SGPT and SGOT showing maximum frequency of derangement in severe category, 72.72% (n=16) and 86.36% (n=19) respectively. Among the 20 cases of Plasmodium falciparum studied, also, maximum frequency of derangement

is seen in severe parasitemia in all the liver function parameters except SGPT, which shows more derangement in moderate parasitemia with all the cases involved (100%, n=4). In all the cases of malaria studied, all the three parameters show increased frequency of derangement with increase in parasite load, with most frequent derangement seen in severe parasitemia. Bilirubin- 50% (n=18), SGPT- 80.55% (n=29) SGOT-83.33% (n=30). While comparing vivax and falciparum malaria, all the LFTs studied show greater derangement in Plasmodium Falciparum when compared to Plasmodium vivax, with greatest difference seen in bilirubin levels. Al-Salahy et al demonstrated significant increase in mean activity enzyme values of SGOT, SGPT and ALP as well as serum bilirubin. [23]

Khuraiya et al obtained nearly similar mean values for both SGPT and SGOT. [24] However, in most studies like the ones by Arevalo- Herrera et al, Al-Salahy et al as well as the present study, mean derangement was observed more in SGOT compared to SGPT. [23,25] This was exactly opposite to the observation of Godse et al where the mean SGPT was more deranged compared to SGOT. [26] In all the cases of malaria studied, all the three parameters show increased frequency of derangement with increase in parasite load, with most frequent derangement seen in severe parasitemia. Bilirubin- 50% (n=18), SGPT- 80.55% (n=29) SGOT-83.33% (n=30). The mean values (±SD) of all the liver functions at various parasitemia levels in malaria. Talking about the liver function parameters, i.e., bilirubin, SGPT and SGOT, all show significant increase in mean values i.e., more derangement with increase in parasitemia (p values being 0.0004, 0.0022 and 0.0048 respectively). All the three parameters show maximum derangement in severe parasitemia with mean values of 3.52, 82.18, and 94.6. While comparing vivax and falciparum malaria, all the LFTs studied show greater derangement in Plasmodium falciparum when compared to Plasmodium vivax, with greatest difference seen in bilirubin levels.

However, the present study observed a different result here where the mean bilirubin values were significantly higher in Plasmodium falciparum compared to Plasmodium vivax. This indicated that hyperbilirubinemia in our study subjects was not just due to hemolysis but also due to hepatocellular damage. Arevalo-Herrera et al also stated that in severe malaria, hepatic dysfunction and alteration of liver enzymes was more frequent and so more derangement is observed in SGOT and SGPT in Plasmodium falciparum cases compared to Plasmodium vivax. [25] The mean values (±SD) of all the liver functions in Plasmodium vivax and Plasmodium falciparum. In the liver function parameters, all the three parameters were significantly raised in Plasmodium falciparum as compared to Plasmodium vivax with the p values of all three being <0.0001.

## Conclusion

Hence, we concluded that altered liver function in form of hyperbilirubinemia and increased liver enzymes in a patient with acute febrile illness increase the probability of malaria, hence directing the clinician along the correct path of further work-up and accurate treatment.

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